

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
METHYL PARATHION

Chemical Code # 000394, Tolerance # 00121  
SB 950 # 043

November 3, 1986

Revised 10/18/89; 1/19/90; 5/23/90; 7/2/90; 12/1/92; 10/31/95; 5/6/96, 11/19/97, 11/25/98, 1/20/04

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect.
Chronic, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, possible adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, possible adverse effect.
Chromosomal aberration:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	No data gap, no adverse effect.

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Toxicology one-liners are attached.

All studies identified through document 0174 208922 have been examined.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T04/01/20 Revised by: G. Chernoff, 7/2/90; Kishiyama & Silva, 12/1/92; Silva, 10/31/95 & 5/6/96; Aldous (minor editing during revision to current software: no new data and no fundamental changes in content), 9/24/97. Revised 11/19/97 by J. Gee; M. Silva, 11/25/98 & 1/20/04

These pages contain summaries only. Individual worksheets may identify additional effects.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

### COMBINED, RAT (Chronic/Oncogenicity)

#### Subchronic, Rat:

**099 127031** "A Three Month Feeding Study of Methyl Parathion in Rats," (I. W. Daly & W.E. Rinehart; Project #: 77-2059 (BD-78-9); Bio/dynamics, Inc., East Millstone, NJ; 2/28/80). Methyl parathion (93.65% pure) was fed in diet to Sprague-Dawley CD rats (20/sex/dose) at 0, 2.5, 25 and 75 ppm for 3 months. Systemic NOEL = 2.5 ppm (At 75 ppm, 14 females and 1 male died or were sacrificed moribund during the first 4 weeks on study. All females and 5/20 males showed tremors, emaciation and staining of the anogenital area at 75 ppm. Body weights were decreased and food consumption was increased in both sexes at 75 ppm. Erythrocytes, hemoglobin and hematocrit were decreased and SGOT was increased in females at 75 ppm. Alkaline phosphatase was increased at  $\geq 25$  ppm. BUN was increased while glucose, total protein, albumin and globulin levels were decreased in females at 75 ppm. Males showed decreased globulin, total protein and glucose levels at 75 ppm. Specific gravity in urine was elevated in both sexes at 75 ppm and associated with positive urinary protein determinations of 100 mg/dl or greater in most animals. Male and female organ weights were reduced as follows: testes/ovaries (5%, 22%), heart (8%, 12%), kidneys (10%, 13%) and liver (15%, 26%) at 75 ppm. In addition, relative (organ/brain & organ/body weight) were increased due to decreased terminal body weights. Lesions in the non-glandular mucosa (discolored areas/foci, raised white areas and abrasions, black/brown tar-like gastric contents) occurred in both sexes at 75 ppm. In addition, acute ulcerative gastritis, lymphoid depletion and necrosis (lymph nodes, spleen & thymus), necrosis of the submaxillary salivary glands and hypocellularity of the bone marrow occurred in both sexes at 75 ppm.) Cholinesterase NOEL = 2.5 ppm (RBC and plasma Cholinesterase levels in both sexes were decreased at  $> 25$  ppm. Brain Cholinesterase was decreased in females at  $> 25$  ppm and males at 75 ppm. **Possible adverse effect.** The data are supplemental. M. Silva, 10/17/95.

#### Combined, rat:

**\*\* 042 011168, 045-050 034227-034232, 098 126319**, "Two Year Chronic Feeding Study of Methyl Parathion in Rats", (Biodynamics, 12/22/83). Methyl parathion (93.65% pure) was fed in diet to Sprague-Dawley (CD) rats (60/sex/group) at 0, 0.5, 5.0 and 50 ppm for 25 months (males) or 28 months (females). Systemic NOEL = 5.0 ppm (Decreased body weight gain was observed in both sexes at 50 ppm. Increased food consumption was observed at  $> 5.0$  mg/kg. Clinical signs, including alopecia, anogenital staining and tremors at 50 ppm and altered gait at  $\geq 5.0$  ppm were observed in females. There was an increased incidence in posterior subcapsular cataracts and retinal degeneration at 50 ppm in both sexes. In addition, females showed decreased Hb and both sexes showed decreased HCT and RBC's at 50 ppm. Histopathologically, both sexes showed peripheral (hindlimb) neuropathy by demyelination of the proximal and distal sciatic nerves at 50 ppm.) Cholinesterase NOEL = 5.0 ppm (Significant decreases in plasma and brain cholinesterase were observed at 50 ppm.) **Possible adverse effects:** Significant brain cholinesterase inhibition and peripheral neuropathies occurred at 50 ppm. Retinal degeneration and posterior subcapsular cataracts occurred in females at 50 ppm. NOTE: Record #011168 has been examined several

times, with associated changes in acceptability status. The study was initially submitted and found adequate to fill the data gap for a chronic toxicity (Schreider, 3/18/85). Upon submission of additional information (034227-034232), this study was then reviewed as a combined (chronic/oncogenicity) study and considered to be unacceptable but upgradeable (Christopher, 10/7/85). Subsequently, the reports were re-reviewed and the status was still unacceptable, based on animal husbandry problems (see 11/24/92 review sheet by M. Silva for details). After submission of the information requested in the 1992 review, and in consideration of the data in several long-term rat studies, this study has been upgraded to **acceptable** with deficiencies as previously noted (see worksheet by M. Silva, 10/3/95).

EPA ONE-LINER: Oncogenic NOEL > 50 ppm (HDT). Neurologic NOEL not defined. Degenerative changes of sciatic nerve in males at high dose level. Thickening of myelin sheaths in high dose females. NOEL (except for neurologic changes) = 0.5 ppm (abnormal gait, slight to moderate decreases in mean hemoglobin, hematocrit and erythrocyte levels in males at 24 months). Effects at 50 ppm include greater incidence of alopecia (particularly in females), bilateral retinal degeneration (females only). CORE grade: minimum (oncogenicity) and supplementary (2 year feeding).

121 - 0172 208916 "Reevaluation of Neuropathology Slides from A Two-Year Chronic Feeding Study of Methyl Parathion in Rats," (O'Shaughnessy, D.; BioDynamics Study #: 77-2060; D. O'Shaughnessy Consulting, Inc., Sparta, NJ; 2/8/02). This volume stated that "The morphometric results of the original report were incorrectly derived and interpreted and should be discounted." It was also stated that "A thorough qualitative examination of nervous system slides of high dose and control animals from both special neurotoxicity and routine pathology subgroups provides good evidence that methyl parathion did not cause any dose-related neuropathological effects at any dose tested." Reevaluations were performed by a private pathology consultant (O'Shaughnessy Consulting, Inc.) that is not held to the guidelines of an EPA selected Pathology Working Group. The data are therefore supplemental. No worksheet. M.Silva, 1/16/04.

**091 089191**, "A Twelve Month Oral Toxicity Study of Methyl Parathion (E 120) in the Rat Via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects". (I. W. Daly, Bio/dynamics, Inc., Project No. 873208, 1/7/91). Methyl Parathion (purity = 94.6%) was administered in the feed at concentrations of 0 (acetone), 0.5, 2.5, 12.5, or 50.0 ppm to Sprague-Dawley rats (70/sex/group) for at least 12 months. A group scheduled to serve 3 months in recovery was canceled. Systemic NOEL = 2.5 ppm [Decreased body weight gain was observed in both sexes at 50 ppm. Increased food consumption was observed, primarily in females, at  $\geq 12.5$  mg/kg. Clinical signs, including aggressiveness, tremors, scabs, sores, and altered gait (primarily females) were observed at 50 ppm.] Cholinesterase NOEL = 2.5 ppm [Plasma Cholinesterase was inhibited significantly in both sexes at 50 ppm. RBC Cholinesterase was inhibited slightly (no greater than 19.5%) at 50 ppm. Brain Cholinesterase was inhibited significantly at 50 ppm in males and at  $\geq 12.5$  ppm in females.] Neurotoxicity NOEL = 0.5 ppm (there was an increase in peripheral neuropathy at  $\geq 12.5$  ppm in both sexes). In addition, there was an increase in proximal sciatic and tibial/peroneal nerve myelin bubbles at > 2.5 ppm in both sexes. Ophthalmological exams performed at month 12 (retina and optic nerve) failed to show treatment related effects. **NOTE: retinal degeneration and posterior subcapsular cataracts were reported at 50 ppm in an earlier chronic study** (DPR Record #11168), occurring at both 24 and 28 months. Not Acceptable (Not a FIFRA Guideline study). Considered to be supplemental only. Kishiyama & Silva, 11/13/92.

121 - 063 076585 (This is the protocol for Record No. 089191, above).

121 - 0170 208911 "Pathology Re-Evaluation; A 12-Month Oral Toxicity Study of Methyl Parathion (E120) in the Rat Via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects," (O'Shaughnessy, D.; Cheminova A/S, Lemvig, Denmark; 3/21/01). In this report of the reread of neuronal pathology from the 12-month study reviewed by DPR (DPR volume/record #: 121 - 091/089191), Dr. O'Shaughnessy recommended a complete reread by an independent expert in toxicologic neuropathology. A report amendment was considered warranted. Information is supplemental. No worksheet. M. Silva, 1/14/04.

121 - 0171 208914 "Methyl Parathion: A Review of the One Year Rat (Daly 1992B) and the 2 Year Rat (Daly 1983) Feeding Studies," (Foster, J.R.; Cheminova Agro, DK; Report #: CTL/P/5696; Final report dated: 1997). This volume contains an analysis of previous studies and data from the 12 month and 2 year rat feeding studies with methyl parathion. Conclusions were as follows:

- Methyl parathion inhibits AchE
- At high doses and at high cholinesterase inhibition clinical symptoms of cholinergic block occur.
- Clinical symptoms are reversible when exposure to methyl parathion is discontinued.
- Methyl parathion does not cause OPIDN
- Exposure to high doses of methyl parathion induces neuropathological changes consistent with demyelination in the peripheral nervous system. These changes are a consequence of the prolonged high level inhibition of AChE and have a threshold dose response and a clear NOEL. These data are supplemental. No worksheet. M. Silva, 1/16/04.

121 - 0173 208918 "A Two-Year Chronic Feeding Study of Methyl Parathion in Rats," (Jortner, B.S.; BioDynamics Study #: 77-2060; Blacksburg, VA; 10/9/02). This volume contains a slide re-read of sections of spinal cord, cauda equina, and peripheral nerve from the BioDynamics Study #: 77-2060 performed by a veterinary neuropathologist. The 2 components of the study were Special Neuropathology and Regular Study components, comparing high dose and control rats. No treatment related alterations were observed in the Special Neuropathology portion of the study. The Regular Study slides could not be evaluated due to the histological quality of the sections. These data are supplemental. The slides were reviewed by an independent laboratory and were not reevaluated according to an EPA Pathology Working Group regulations. No worksheet. M. Silva, 1/16/04

121 - 0174 208922 "Review of Existing Studies with Neuropathological Evaluation of Rats Treated with Methyl Parathion and Conclusions Regarding the Potential for Methyl Parathion to Cause Peripheral Neuropathy," (O'Shaughnessy, D.; D. O'Shaughnessy Consulting Inc., Sparta, NJ; 6/17/02). This volume contains the argument that earlier studies examining neuropathology were limited by the specialized and detailed neuropathology directed by (then) new guidelines. "Both technical preparation of tissues with perfusion fixation, osmium post-fixation and epoxy plastic embedding and sectioning, as well as recognition by pathologists of the enhanced morphology of lesions or of artifacts introduced by and made more visible by the technical changes and their shortcomings, made reporting of these studies less certain." Due to the specialized nature of the slide preparation and evaluation, this report (including open literature studies) was put forth to assist readers in understanding the technical and interpretational issues involved. These data are useful, but supplemental. No worksheet. M. Silva, 1/16/04

131 164089 "Re-evaluation of Selected Peripheral (Sciatic and Tibial) Nerve Tissues from a Previously Submitted Chronic Toxicity Study of Methyl Parathion to Rats [Huntingdon Life Sciences (formerly Bio/dynamics, Inc.) Project #87-3208; Study #3189-346, MRID 418538-01]," (Brennecke, L.H., Pathology Associated International; Cheminova Agro A/S, Lemvig, Denmark; Jellinek, Schwartz

& Connolly, Inc., December 30, 1996). The author concluded there were no treatment-related effects. The re-read of the slides did not conform with EPA guidelines for a Pathology Working Group (PWG). These data were considered supplemental. No worksheet. M. Silva, 11/25/98.

#### CHRONIC TOXICITY, RAT

**051, 052, 063 037188, 037189, 074202**, "E 605 - Methyl (Parathion-methyl) Chronic Toxicological Study on Rats (Feeding Experiments Over Two Years)"; (Bayer, 3/31/81). Methyl parathion (94.8%) fed in the diet at 0, 2, 10 and 50 ppm for 2 years; 50/sex/group; plasma and RBC cholinesterase inhibition indicated adequate dosing; blood chemistry measurements indicated liver and kidney effects at the high dose level, no evidence of oncogenicity effects; NOEL = 2 ppm (cholinesterase effects); initially reviewed as unacceptable (no diet analysis to verify levels of test article, needed frequency and description of diet preparation, spinal cord and peripheral nerves not examined by histopathology, needed summary tables with actual number of tissues examined, no clinical observations on individual animals); but upgradeable (Remsen, 12/6/85). Record # 074202 contains diet analyses and stability (temperature and conditions not stated), individual clinical observations for a limited number of animals and individual gross autopsy findings. Still UNACCEPTABLE. Now not upgradeable. Gee, 10/16/89.

EPA One liner: Core Grade Supplementary as a chronic study; Core Minimum as an oncogenicity study.

#### CHRONIC TOXICITY, DOG

**\*\* 132 164091** "One Year Oral (Dietary) Toxicity Study of Methyl Parathion in Dogs," (Hatch, R.C., MPI Research, Mattawan, MI; Lab ID #: 668-003; 9/4/98). Methyl Parathion (95.8% pure) was fed in diet to beagle dogs (4/sex/dose) at 0, 0.3, 1.0, 3.0, 3.5 and 4 mg/kg/day at the beginning of the study. After 3 months on study, the 3.0 mg/kg/day group was placed on recovery (given untreated diet) for 30 days and then euthanized and discarded after measuring intraocular pressure. In addition, at this time 2 of the 4.0 mg/kg/day females were moved to the 3.5 mg/kg/day group and 2 of the 3.5 mg/kg/day males were moved to the 4.0 mg/kg/day group. The remaining 4.0 mg/kg/day females (2 dogs) and 3.5 mg/kg/day males (2 dogs) which were not transferred to other groups were euthanized and discarded. Systemic NOEL = 1.0 mg/kg--Females; 1.0 mg/kg--Males (Clinical signs: males at 4.0 mg/kg showed an increase in diarrhea and thinness and a female at 3.5 mg/kg developed clinical signs of epilepsy (this effect may have been idiopathic). Some biochemical parameters (calcium, albumin, total protein) were intermittently decreased in males (6-12 months) at 4.0 mg/kg/day. Females had decreased calcium, total protein, albumin and globulin were observed at 4.0 mg/kg/day (6 months--not measured at 12 months). Relative (adrenal/brain% x 10<sup>3</sup>) adrenal weights were increased in a dose-related manner (significant at 4.0 mg/kg/day) after 12 months. Females at 3.5 mg/kg showed significantly decreased, dose-related absolute and relative spleen weights after 12 months. Males (2/4) at 4.0 mg/kg showed mild lymphoid cell depletion in the thymus gland after 12 months. Females showed pituitary gland cysts (mild) at 12 months, primarily at 3.5 mg/kg/day.) ChE NOAEL = 0.3 mg/kg (Males showed significantly inhibited Plasma ChE at 0.3 mg/kg. Plasma and RBC ChE were significantly decreased in both sexes at  $\geq 1.0$  mg/kg throughout the study.) Brain ChE NOEL = 1.0 mg/kg (Males showed significantly decreased caudate nucleus ChE at 4.0 mg/kg.) There were no treatment-related ophthalmological effects, including intraocular pressure and electroretinograms. Acceptable. M. Silva, 11/12/98.

040 011166, "Methyl Parathion: One Year Dog Study", (Pharmacopathics, 8/21/81). Methyl parathion (93.65%) in the diet at 0, 0.03, 0.1 and 0.3 mg/kg/day for one year; 8/sex/group; no effects noted; NOEL = 0.3 mg/kg/day (HDT); UNACCEPTABLE (MTD not achieved, incomplete histology); NOT UPGRADEABLE. Schreider, 3/20/85. In addition, this study is not acceptable since no ophthalmology was performed.  
EPA One liner: Core Grade Supplementary.

098 No record number: Response to DPR review of the chronic dog study on methyl parathion. No worksheet, no data. M. Silva, 10/3/95.

070, 085; 090468, "A 13-Week Subchronic Toxicity Study of Methyl Parathion in Dogs Via the Diet Followed by a One-Month Recovery Period", (I.W. Daly, Bio/dynamics, Inc., Project No. 87-3209, 11/20/89). Methyl Parathion, 94.9%, lot #233690479, was administered in the diet to groups of 8 beagle dogs per sex at treatment levels of 0 (diet only), 0.03, 0.30, or 3.0 mg/kg/day for 13 weeks. At the end of the treatment period, 4 dogs per sex per group were terminated, and the remainder were placed on the control diet for a 4 to 6 week recovery period. Ophthalmoscopic, tonometric, and electroretinographic examinations were conducted, and cholinesterase levels measured, prior to, during, and after the treatment period. Plasma, RBC, and brain cholinesterase levels were consistently decreased at 3.0 mg/kg/day during the treatment period. Intra-ocular pressure was sporadically decreased (mid-dose females and high dose males) only in the recovery period. Systemic NOEL = 0.03 mg/kg/day (decreased intra-ocular pressure); Systemic NOAEL > 3.0 mg/kg/day; Cholinesterase NOEL = 0.3 mg/kg/day. This is ACCEPTABLE AS A SUPPLEMENTAL STUDY, and no adverse effect is indicated (G. Chernoff, 5/22/90).

065 073970, 073974, Supplemental to 090468; draft study design and protocol; no worksheet (Gee, 10/16/89).

SUMMARY: The subchronic study (DPR No. 090468) was submitted for consideration in filling the deficiencies noted in the chronic study (DPR No. 011166), specifically, the concern regarding the lack of an MTD. In the subchronic study, significant plasma, RBC, and brain cholinesterase depression effects were observed at 3.0 mg/kg/day. This dose is 10 times greater than the high dose used in the chronic study (0.3 mg/kg/day). DPR now finds there are sufficient data to fill the chronic dog data gap. M. Silva, 5/2/96.

088 095250 "Data Evaluation Record, Methyl Parathion, Subchronic Oral Toxicity Study in Dogs," (Weir, R.J., EPA evaluation of the subchronic dog study, 9/18/90). This information was submitted to show that EPA had waived further requirements for a chronic dog study. M. Silva, 11/24/92.

No record number, pages only: A letter dated 9/11/90, from Cheminova was a request that DPR not make further decisions about methyl parathion in chronic dog studies until the US-EPA review had been received and evaluated. M. Silva, 11/24/92.

114 145815-145818 "Material in Support of Request for Reconsideration of Acceptability of Dog Chronic Toxicity Data," was submitted by Cheminova, Ltd., as a rebuttal document (March 27, 1996). No worksheet. M. Silva, 4/17/96.

118 150561 Twelve page 3-month interim report on a 1-year dog study with methyl parathion in beagle dogs initiated at MPI Research on April 30, 1996. The report, dated October 18, 1996, contains preliminary data on plasma and RBC cholinesterase inhibition and summary and individual data on intraocular pressure. Doses were 0, 0.3, 1.0, 3.0, 3.5 and 4.0 mg/kg. The mid-dose group of

3.0 was taken off treatment after 3 months and fed control diet for a 4 week recovery period. Cholinesterase was significantly inhibited at  $\geq 1.0$  mg/kg. No effect on intraocular pressure was noted up to the 3-month measurement. No worksheet. J. Gee, 11/19/97.

119 153151 Four page summary of results on the 1-year dog study with data for plasma and RBC cholinesterase results for 1, 3 and 6 months. See # 150561 for additional details. No worksheet. J. Gee, 11/19/97.

#### ONCOGENICITY, RAT

038 049211, "Bioassay of Methyl Parathion for Possible Carcinogenicity (Rats)", (Litton for NCI, 1979). Methyl parathion (94.6%) fed in the diet at 0, 20 and 40 ppm for 102 weeks; 20/sex in control group, 50/sex/treated group; decreased survival in females at high dose level; insufficient information to gauge potential adverse effects; insufficient data to set a NOEL; unacceptable (only two dose levels, no analysis of diet for test article, inadequate number of control animals, no analysis of time to tumor, no measurement of food consumption, no pathology summary, no hematology or blood chemistry), NOT UPGRADEABLE. Schreider, 3/21/85.  
EPA 1-liner: Core Grade Supplementary. Not carcinogenic.

#### ONCOGENICITY, MOUSE

\*\*094 098865, "Methyl Parathion: Study for Chronic Toxicity and Carcinogenicity in B6C3F1 Mice," (R. Eiben, Bayer AG Fachbereich Toxikologie, Study No.: T4027023, May 17, 1991). Methyl parathion (E120 technical grade, purity = 95.5%) was administered in the feed at concentrations of 0 (peanut oil), 1, 7, or 50 ppm to 15 or 50 B6C3F1 mice/sex/group for 52 or 104 weeks, respectively. Cholinesterase NOEL = 1 ppm/day based on inhibition of RBC Cholinesterase at  $\geq 7$  ppm and inhibition of plasma and brain Cholinesterase at 50 ppm. Systemic NOEL = 7 ppm based on increased body weights with decreased food consumption and increased liver and kidney weights in both sexes at 50 ppm. A treatment-related oncogenic effect was not observed in this study. Acceptable with no adverse effect. J. Kishiyama & M. Silva, 11/24/92.

038 927589 "Bioassay of Methyl Parathion for Possible Carcinogenicity (Mouse)", (Litton for NCI, 1979). Methyl parathion (94.6%) fed in the diet at 0, 62.5 and 125 ppm (changed to 20 and 50 ppm at week 37) for 102 weeks; 20/sex in control group, 50/sex/treated group, B6C3F1 mice; no adverse effects reported; NOEL cannot be established; UNACCEPTABLE (only two dose levels, no analysis of diet for test article, inadequate number of control animals, no analysis of time to tumor, no pathology summary, no hematology or blood chemistry, no food consumption data), NOT UPGRADEABLE. Schreider, 3/21/85.  
EPA 1-liner: Core Grade Supplementary. Not carcinogenic.

086 088521, "Oncogenicity Feeding Study in Mice With E-120", (Bayer Study No. T4027023). Protocol for new study (see Record No. 098865, above). No worksheet (G. Chernoff, 7/2/90).  
086 088522, "Pilot Dose-Finding Study for a Carcinogenicity Study in B6C3F1 Mice, Administration in the Feed Over 66 Days", (Eiben, R., Bayer AG, Study No. T5025378, 7/87). Results of a range finding study. No worksheet (G. Chernoff, 7/2/90).

086 088523, "Pilot Dose-Finding Study for a Carcinogenicity Study in B6C3F1 Mice, Administration in the Feed Over 65 Days", (Eiben, R., Bayer AG, Study No. T1025518, 7/87). Results of a range finding study. No worksheet (G. Chernoff, 7/2/90).

## REPRODUCTION, RAT

**\*\*044 011171**, "Two-Generation Reproductive Study of Methyl Parathion in Rats", (Bio/dynamics, Report No. BD-80-139, 7/18/82). Methyl parathion, 93.6% pure, was given in the diet to Sprague-Dawley CD rats (15 males & 30 females/group) at 0 (acetone = vehicle), 0.5, 5.0 and 25 ppm for two generations (one litter/generation). Maternal NOEL = 5 ppm (marginal decrease in weight gain at the end of lactation); Maternal NOAEL > 25 ppm; Reproductive NOEL and NOAEL = 5 ppm (decreased pup survivability). Formerly reviewed as unacceptable (Schreider, 3/18/85) for no justification of dose levels, no characterization of test article, no litter standardization, and incomplete histopathology. The study was upgraded to ACCEPTABLE (M. Silva, 1/19/90) based on an EPA Memorandum resulting in a re-review of the study. Another reevaluation of the study, prompted by the rebuttal in Record No. 086795, resulted in the decreased pup survivability being identified as a POSSIBLE ADVERSE HEALTH EFFECT (G. Chernoff, 5/21/90).  
EPA One liner: Core Grade Minimum.

081 086795, Supplemental to 011171; rebuttal arguments (G. Chernoff, 5/21/90).

**053 037190, 037191**, "E 605-Methyl (Methyl Parathion) Multigeneration Studies on Rats (Reproduction)", (Bayer, 2/8/82). Methyl parathion (95%) was given in the diet at 0, 2, 10 and 50 ppm for a three generation study; 10 males/group, 20 females/group. There were no pups surviving at the end of F2 generation in the high dose group; NOEL = 2 ppm; UNACCEPTABLE (needs QA statement and final report revisions, no analysis of diet for test article, food consumption not measured, no clinical observations. presented, incomplete necropsy data, gestation and lactation weights included in weekly female weights), NOT UPGRADEABLE. Parker, 12/5/85.

**033 927643**, "Methyl Parathion - Monograph Number Seven - Environmental Health Evaluation of California Restricted Insecticides (Toxicological Evaluations)", (P.M. Dolinger Assoc., 1979?, page 51). Summary of 3-generation study using methyl parathion (10 and 30 ppm in the diet) conducted by Woodard Research Corp. Reductions in survival noted for Fla, F1b, and F2a generations at 30 ppm and in the F-3a generation at 10 ppm; stillbirth rates were increased in F1b and F3b generations at 30 ppm; UNACCEPTABLE (no data), NOT UPGRADEABLE.  
EPA One liner: Core Grade Supplementary.

SUMMARY: A consistent finding in the three rat reproduction studies on file was a decrease in pup survivability. In two of the studies (#Is 927643 and 037190) where the doses included 0, 2, 10, 30 and 50 ppm, decreased survivability was observed at 10 ppm. In the third study (#011171) where the doses were 0, 0.5, 5.0, and 25 ppm, survivability was decreased at 25 ppm. Taken together, these data indicate decreased pup survivability is a consistent possible adverse effect with a NOEL = 5 ppm (Chernoff, 5/23/90).



## TERATOLOGY, RAT

**\*\*068 085036**, "Embryotoxicity (Including Teratogenicity) Study with E120 TECHNICAL (Common Name: PARATHION-METHYL) in the Rat" (Research and Consulting Company AG, RCC 083553, 12/31/87). Technical methyl parathion, batch 230 606 003, 97% pure in 0.5% aqueous Cremophor EL was administered by oral intubation to groups of 25 mated Wistar/HAN female rats at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6 through 15 of gestation. An additional 10 females each were added to the 0 and 3.0 mg/kg/day groups for cholinesterase activity measurement.

**Possible adverse effects:** Decreased maternal cholinesterase activity, maternal signs of organophosphate toxicity, decreased maternal weight gain, decreased maternal food consumption, fetal developmental delay determined by decreased fetal weight and delayed ossification, and a tendency toward increased resorptions, all at 3.0 mg/kg/day. Maternal NOEL = 1.0 mg/kg/day (signs of organophosphate toxicity, cholinesterase inhibition, decreased food consumption and weight gain). Developmental NOEL = 1.0 mg/kg/day (developmental delay and marginal increase in resorptions). ACCEPTABLE study. G. Chernoff, 10/12/89.

055 037196, "Parathion-Methyl Evaluation For Embryotoxic and Teratogenic Effects on Rats Following Oral Administration", (Bayer, 6/3/77). Methyl parathion (94.4%) by oral gavage at 0, 0.1, 0.3 and 1.0 on days 6-15 of gestation; 20 pregnant females/group; fetal body weight decreased in high dose group; NOEL cannot be determined; UNACCEPTABLE (need analysis of dosing solution; need individual data for body weight, food consumption, necropsy parameters, fetal exams, fetal weights and clinical observations.), POSSIBLY UPGRADEABLE. Parker, 12/4/85.  
EPA One liner: Core Grade Supplementary.

031 927582, EPA summary of study identified as record #037196.

033 038392, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Teratogenicity, Mammalian Rat Studies", (Dolinger Assoc. Report, pages 48-49). Summary of journal article by Fish (1966) in which rats were injected i.p. with methyl parathion on day 9 or 15 of gestation; insufficient data for evaluation. Study by Tanimura et al. (1967) suggests that one i.p. injection of methyl parathion at 15 mg/kg on day 12 of gestation reduced fetal weight.  
EPA One liner: Core Grade Supplementary.

## TERATOLOGY, RABBIT

095 111287, "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Methyl Parathion Technical Administered Orally via Stomach Tube to New Zealand White Rabbits", (Alan M. Hoberman, Argus Research Laboratories, Inc., Horsham, PA., Report # 310-007, 11/16/91). Methyl parathion technical (95.7% pure) was administered by gavage to artificially inseminated New Zealand White [Hra:(NZW)SPF] female rabbits (19 or 20/group) on gestation days 6 through 18 at 0 (corn oil), 0.3, 3.0, and 9.0 mg/kg/day. Maternal cholinesterase NOEL < 0.3 mg/kg/day (Significant RBC Cholinesterase inhibition occurred at  $\geq$  3.0 mg/kg/day. A significant decrease in plasma Cholinesterase occurred at 9.0 mg/kg/day. Maternal Systemic NOEL: There were no significant maternal effects at any dose. Developmental NOEL = 3.0 mg/kg/day (There was an increased incidence in thickened areas of ossification in the ribs at 9.0 mg/kg/day). **Acceptable, with no adverse effects.** (H. Green & M. Silva, 11/6/92)

055 037197, "Parathion-methyl (Folidol M Active Ingredient) Study for Embryotoxic Effects on Rabbits After Oral Administration", (Renhof, M., Bayer AG Institute of Toxicology, Report No. 12907, 9/4/84). Methyl parathion, 95.7% pure in 0.5% aqueous Cremophor EL emulsion vehicle was administered by oral gavage to groups of 12-15 pregnant Himalayan CHBB:HM rabbits at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6-18 of gestation. No adverse effects were noted. Maternal and Developmental NOEL > 3 mg/kg/day. Initially reviewed as unacceptable but possibly upgradeable with submission of justification of dosing levels, all the individual animal data, a description of the dosing solution preparation, and an analysis of the dosing solution (Parker, 12/4/85). After review of the supplemental information provided in record nos. 085035 and 088518, the study remains UNACCEPTABLE and is now considered not upgradeable due to the lack of a MTD (G. Chernoff, 6/29/90).

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068 085035, "Supplement to Methyl Parathion (EI2O) Study for Embryonic Effects on Rabbits After Oral Administration", (Bayer, 12/22/87). Supplemental to record no. 037197, consisting of a retrospective range finding study in rabbits at doses of 0, 0.3, 1.0, and 3.0 mg/kg/day. The only notable finding was a minimal reduction in RBC cholinesterase activity on days 14 and 19 in the high dose group (G. Chernoff, 7/2/90).

083 088518, "Additional Information to Methyl Parathion Study for Embryotoxic Effects on Rabbits After Oral Administration", (Renhof, M., Bayer AG, Report No. 12907, 12/22/87). Supplemental to record no. 037197, consisting of a dose justification based on a rat teratology study, individual animal data, test compound analysis, and an abbreviated study protocol (G. Chernoff, 7/2/90).

NOTE: Justification for the dose selection used in the rabbit teratology study (DPR Record No. 037197) has been provided in two separate documents. In the first (DPR Record No. 085035), the results of a retrospective range-finding study were presented. The only finding indicative of an MTD was a marginal decrease in RBC cholinesterase levels at 3.0 mg/kg/day, the highest dose tested. Plasma and brain cholinesterase levels were unaffected by the treatment, as were appearance, behavior, weight gain, autopsy findings, and maternal deaths. The second justification (DPR Record No. 088518), was based on the results of an unacceptable rat teratology study (DPR Record No. 037196), in which a maternal MTD was not clearly established. These data for the rat study are considered inadequate, and inappropriate for dose justification in the rabbit study. Since the demonstration of a clear MTD was not achieved in either the original rabbit teratology study, or in the retrospective range finding study, this information is not sufficient to fill the data gap. DPR Record No. 111287 (Argus Research Laboratories, 11/16/91), however, is an acceptable rabbit teratology study and therefore, the data gap is filled. (M. Silva, 12/1/92).

## TERATOLOGY, MOUSE

033 038392, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Teratogenicity, Mammalian Mouse Studies", (Dolinger Assoc. Report, page 49). Summary of journal article by Tanimura et al. (1967) in which mice were injected once i.p. with 20 or 60 mg/kg on day 10 of gestation; in high dose group 13 of 112 fetuses had cleft palate, fetal deaths elevated at the high dose level.

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## GENE MUTATION

**054 037192**, "E120 Parathion-Methyl Salmonella/Microsome Test to Evaluate for Point Mutations (Salmonella Typhimurium)", (Bayer, 8/1/80). Methyl parathion (94.5%) tested at 0, 20, 100, 500, 2500, or 12,500 ug/plate +/- S9 with Salmonella strains TA 1535, TA 1537, TA 98 and TA 100; positive response with TA 1535 with S9 and TA 100 with and without S9; confirmed in repeat experiment; UNACCEPTABLE (no individual plate counts, no controls for -S9 series, unclear description of bacteriostatic activity, incomplete description of methodology), POSSIBLY UPGRADEABLE. Remsen, 12/6/85.

**\*\*054 037193**, "E120 Parathion-Methyl Folidol M Active Ingredient Salmonella/Microsome Test to Evaluate for Point Mutations (Salmonella Typhimurium)", (Bayer, 8/1/80). Methyl parathion (96.1%) tested at 0, 20, 100, 500, 2500 or 12500 ug/plate +/- S9 on Salmonella strains TA 1535, TA 1537, TA 98 and TA 100; positive response in TA 100 and probably TA 98; confirmed with repeat experiments; ACCEPTABLE. See also 37192. Remsen, 12/6/85.

033 038391, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Mutagenicity Microbial Studies", (Dolinger Report, pages 47-48). Summary of several journal articles on the potential genotoxic activity of methyl parathion; insufficient information to evaluate; weakly mutagenic to E. coli at 0.1 M, positive results for mutagenicity in four microbial systems were reported, references were also made to studies with bacterial systems in which methyl parathion did not increase mutation frequency (Schreider, 2/21/85).

## CHROMOSOME EFFECTS

054 037194 "E120 Parathion-Methyl Folidol M - Active Ingredient Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect", (Bayer, 3/29/82). Methyl parathion (95.6%) tested in mouse micronucleus assay at 0, 10 or 20 mg/kg by oral gavage given twice at 24-hour interval; 5/sex/group; animals sacrificed after 6 hrs; 1000 PCE's evaluated; no increase noted, but positive control effective; UNACCEPTABLE (only a 6 hr sampling time, only 2 dose levels with no evidence of toxicity - dose selection based on a pilot study where 2 x 10 mg/kg caused "somnolence"), NOT UPGRADEABLE. Remsen, 12/6/85.

**\*\*054, 064 037195, 074209-212**, "E 120 Parathion Methyl - Dominant Lethal Test on the Male Mouse to Evaluate for Mutagenic Effect", (Bayer AG, 6/7/84). Methyl parathion (95.7%) tested at 0 or 10 mg/kg by oral gavage in mouse dominant-lethal assay; 46 males/group; mated 1:1 for 12 X 4 days; no adverse effect reported; initially reviewed as unacceptable (no positive controls included and no historical controls). Remsen, 12/6/85. Submission of document 121-064 containing three positive control studies with Endoxan in the same strain of mice and a compilation of historical control data in females over a period of years upgrades the study to ACCEPTABLE. Gee, 10/16/89.

031 927582, "Initial Scientific and Microeconomic Review of Parathion: Subpart II. B. Pharmacology and Toxicology", (EPA 540/1-75-001). Summary of a journal article. Single dose of methyl parathion tested on guinea pigs for testicular chromosome aberration. Although potential adverse effect on chromosome abnormalities was indicated, data are inadequate for evaluation. Remsen, 12/6/85.

033 038391, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Mutagenicity Microbial - Studies", (Dolinger Report, page 48). Summary of a journal article by Huang (1973) in which the effect of i.p.-injected methyl parathion on mouse chromosomes was examined; no aberrations were noted in bone marrow chromosomes in a group treated with 20 mg/kg. Remsen, 12/6/85.

### DNA DAMAGE

**\*\*067 075728**, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes - Methyl Parathion", (Microbiologica1 Associates, 6/22/89). Methyl parathion, lot 95IA-84, no purity stated; tested with primary rat hepatocytes from Fischer 344 male rat(s) at 0 (ethanol and medium), 0.0003, 0.001, 0.003, 0.01, 0.02 and 0.03  $\mu\text{l/ml}$  of medium; tritiated thymidine incorporation over 18 - 20 hour incubation by autoradiography; scored 50 nuclei per each of three slides; 0.03  $\mu\text{l/ml}$  was too toxic to score; no evidence of induction of unscheduled DNA synthesis; ACCEPTABLE. Gee, 10/16/89.

### NEUROTOXICITY

**\*\*084 088519**, "Methyl Parathion: An Acute Delayed Neurotoxicity Study in the Laying Hen (Gallus gallus domesticus)", (Beavers, J.B., J. Foster, B.Y. Cockrell and M.J. Jaber, Wildlife International Ltd., Project No. 232-111, May 1, 1990). Methyl parathion technical without xylene, 95.8%, Batch #95-IA-57, was administered to 16 adult hens at an initial dose of 250 mg/kg/day (16% above the LD50) with atropine, followed by a second dose of 215 mg/kg/day on day 21. Six hens died within a few days of the initial dosing, and two died within a few days of the second dosing. There were no deaths reported in the negative (corn oil vehicle) control, or the positive TOCP (600 mg/kg) control. Based on the absence of persistent clinical signs, ataxia, or remarkable histopathological findings, there is no evidence to suggest that methyl parathion causes acute delayed neurotoxicity within the experimental conditions of this study. The study is ACCEPTABLE, and no adverse health effect is noted (G. Chernoff, 6/29/90).

103 129644 This document is an adverse health disclosure for an acute neurotoxicity study with methyl parathion in rats. No worksheet. M. Silva, 10/10/95.

**\*\* 129 164087** "Acute Neurotoxicity Study of Methyl Parathion in Rats," (Minnema, D.J., Hazleton Washington, Inc., Vienna, Virginia; Lab. Project ID #: HWA 2688-102; 5/31/94). Methyl Parathion technical (93.1% pure) was administered in a single gavage dose to Sprague-Dawley Crl:CD<sup>®</sup> BR rats at 0, 0.025, 7.5, 10.0 (males only) and 15.0 (females only) mg/kg. A Functional Operational Battery (FOB) and Locomotor Activity (LMA) were conducted at pre-test and 1.5 hours (time of peak effect), 1 and 2 weeks post-dosing (10/sex/dose). Assessments of plasma, RBC and regional brain cholinesterase were performed at pre-test, 1.5 hours post-dose (all dose groups) and at 2 weeks (control and high dose only). Neurotoxicity NOEL = 0.025 mg/kg (There were increased clinical observations and neurobehavioral effects observed in both sexes at  $\geq 7.5$  mg/kg. Males at  $\geq 7.5$  mg/kg and females at 15.0 mg/kg showed increased incidence and severity of demyelination. Cholinesterase NOEL = 0.025 mg/kg (There was significantly decreased plasma, RBC and brain ChE observed at  $\geq 7.5$  mg/kg in both sexes. At day 14, effects continued at the high dose (low and

mid-doses were not assessed.)) Possible adverse effect (increased demyelination, neurobehavioral effects and significantly decreased ChE). Acceptable. M. Silva, 11/19/98.

121 - 0168 208907 "Pathology Re-Evaluation; Acute Neurotoxicity Study of Methyl Parathion in Rats," (O'Shaughnessy, D.; Hazleton Washington Study 2688-102, 1994; Cheminova A/S, Lemvig, Denmark; 3/21/01). This amendment to the study (DPR volume/record #: 121-129/164087) contains several corrections which do not alter the results or conclusions from the original report. Supplemental data. No worksheet. M. Silva, 1/14/04.

121 - 0169 208909 "Hazleton Study #2688-102 Acute Neurotoxicity Study of Methyl Parathion in Rats. Neuropathology Slide Reread." (Jortner, B.S.; Veterinary Neuropathologist, Blacksburg, VA; 6/19/02). This amendment to the study (DPR volume/record #: 121-129/164087) contains a reread of the pathology slides by Jortner, B., Pathologist. This reread was not performed according to USEPA Pathology Working Group recommendations, the information is considered to be supplemental. No worksheet. M. Silva, 1/14/04.

**\*\* 130 164088** "Subchronic Neurotoxicity Study of Dietary Methyl Parathion in Rats," (Minnema, D.J.; Hazleton Washington, Inc. (HWA), Vienna, VA; Lab Project ID #: HWA 2688-103; 12/19/94). Methyl parathion technical (93.1% pure) was fed in diet to Sprague-Dawley Crl:CD®BR rats (10/sex) at 0, 0.5, 5 and 50 ppm for 13 weeks. Additional animals from the control and high dose animals (5/sex/dose) were designated as recovery (behavioral and cholinesterase) animals (weeks 14 - 17). These animals were also used for a limited FOB testing at weeks 13 & 16 or ChE at week 17. Systemic NOEL = 5.0 ppm (There were increased clinical observations, decreased food consumption and body weights in both sexes at 50 ppm. There were increased effects in the FOB (latency to first step, pupil response, fore-limb and hind-limb grip strength, tremors and other signs) in both sexes at 50 ppm. Alopecia was observed in both sexes at 50 ppm (1/6).) ChE NOEL = 0.5 ppm (Plasma ChE was significantly decreased in males at 50 ppm and in females at  $\geq 5.0$  ppm. RBC ChE was significantly decreased in both sexes at  $\geq 5.0$  ppm. Regional brain ChE was significantly decreased in males at  $\geq 5.0$  ppm and in females at 50 ppm.) No histopathological findings, including degenerative lesions, were reported. Possible adverse effect: Significant decrease in RBC and brain ChE, which, in some cases, did not return completely to control values after the recovery period. Acceptable. M. Silva, 11/25/98.

**\*\* 121 - 164 186610** "A Developmental Neurotoxicity Study of Orally Administered Methyl Parathion in the Rat," (Beyrouthy, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID#: 97574; 3/1/02). Methyl parathion (96.8% pure) was administered by gavage to mated Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (32/dose) at 0 (corn oil), 0.03, 0.3 and 0.6 mg/kg from gestation day 6 to lactation day 10 and their offspring were treated by oral gavage at the same dose levels from day 11 to 21 *post partum*. Pups were allowed to grow to adulthood, then were tested for behavioral/activity/neurotoxicity effects at 60 days, then terminated at 70 days of age. Maternal NOEL = 0.3 mg/kg (F0 generation had increased salivation at 0.6 mg/kg.) Pup NOEL = 0.3 mg/kg (F1 pups at 0.6 mg/kg showed tremors and salivation post dosing.) Untreated F1 adult NOEL > 0.6 mg/kg (Effects observed in F1 pups/weanlings were not observed in adults when tested at 60 days of age or at termination (70 days).) Cholinesterase activity was not measured. There were no treatment-related differences in brain measurements, observational battery or motor activity. No adverse effect. Acceptable. M. Silva, 5/24/02

121 - 0166 208898 "Positive Control Data from ClinTrials BioResearch Laboratory relevant to the Methyl Parathion Developmental Neurotoxicity Study," (Beyrouthy, P., Robinson, K., ClinTrials

BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID #s: 35109, 95353, 95352.1; 9/24/02). This volume was submitted in support of the definitive developmental neurotoxicity study in rat (DPR volume/record #: 121 - 164/186610), reviewed by DPR. These are supplementary data. No worksheet. M. Silva, 1/14/04.

121 - 125 164083 "Comments from Cheminova Agro A/S on California Department of Pesticide Regulation's Evaluation of Methyl Parathion as a Toxic Air Contaminant," (Reiss, R., Severn, D.J. and Neal, B.; Cheminova Agro A/S, Lemvig, Denmark; Jellinek, Schwartz & Connolly, Inc., October 20, 1998). This is supplemental information relevant to risk assessment for methyl parathion. No worksheet. M. Silva, 11/25/98.

121 - 0165 208894 "Cheminova's Response to a Draft Risk Assessment for Methyl Parathion Prepared by the California Department of Pesticide Regulation," (Cheminova A/S, Lemvig, Denmark; 12/19/03). This volume contains a response to various issues put forth in the DPR draft risk assessment for methyl parathion. This information is supplemental. No worksheet. Silva, 1/14/04

121 - 0167 208904 "Methyl Parathion - Review of Dermal Penetration Study in Rats (MRID #: 45471801)," (Shah, P.V., 5/29/02). This volume contains an EPA review of dermal penetration for methyl parathion. Nominal doses of [<sup>14</sup>C-U ring]-methyl parathion were 1 and 12 ug/cm<sup>2</sup> (equivalent to 0.04 and 0.46 mg/kg body weight) with a dose exposure of 10 hours with a post-dose period of 4 days. Results of the applied dose ranged from 81.4% to 96.6% recovery. At both low and high doses, the dermal penetration of radioactivity was rapid. Absorption (Sum of cage wash, urine, feces, carcass) averaged 84.4 (± 7.6%) for the low dose and 79.4 (± 3.9%) for the high dose. Little remained in skin (including exposed skin and skin under the protective device) 10 hours post-dosing (1.4 - 2.6%) and < 1% remained in the carcass. Excretion was primarily in the urine (78% low dose; 81.8% high dose). Greater than 96% of the absorbed dose was recovered in the urine of every animal. Feces contained a mean of 0.70% (low dose) and 1.4% (high dose) of the applied dose. These data are supplemental. M. Silva, 1/20/04.